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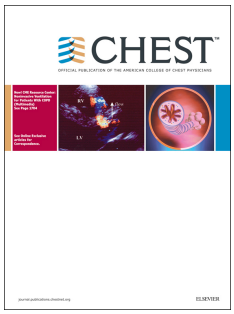

Reference values for peak exercise cardiac output in healthy individuals

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Reference values for peak exercise cardiac output in healthy individuals.

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ABSTRACT

Aims: Cardiac output (Q) is a key parameter in the assessment of cardiac function, its measurement being crucial for the diagnosis, treatment and prognostic evaluation of all heart diseases. Until recently, Q determination at peak exercise has been possible through invasive methods, so that normal values were obtained in studies based on small populations.

Methods and Results: Nowadays, peak Q can be measured noninvasively by means of inert gas rebreathing technique (IGR). The present study was undertaken to provide reference values for peak Q in the normal general population and to obtain a formula able to estimate peak exercise Q from measured peak oxygen uptake (VO_2).

We studied 500 normal subjects (age 44.9±1.5 years, range 18-77, 260 males, 240 females) who underwent a maximal cardiopulmonary exercise test with peak Q measurement by IGR.

In the overall study sample, peak Q was 13.2±3.5 L/min (males: 15.3±3.3 L/min; females: 11.0±2.0 L/min, $p<0.001$) and peak VO_2 was 95±18% of the maximum predicted value (male: 95± 19%; female: 95±18%). Peak VO_2 and peak Q progressively decreased with age (R^2: 0.082, $p<0.001$ and R^2: 0.144, $p< 0.001$, respectively). The VO_2-derived formula to measure Q at peak exercise was (4.4 x peak VO_2) + 4.3 in the overall study cohort, (4.3 x peak VO_2) + 4.5 in males and (4.9 x peak VO_2) + 3.6 in females.

Conclusions: The simultaneous measurement of Q and VO_2 at peak exercise in a large sample of healthy subjects provided an equation to predict peak Q from peak VO_2 values.

INTRODUCTION

A reduction of exercise capacity is frequently reported as the cause of medical assessment in apparently healthy subjects, and it may be due to several reasons, but most often to low cardiac output (Q) and/or low muscle conditioning. The evidence of a low peak exercise Q is therefore of paramount importance in separating subjects with deconditioning from those with heart failure (HF), and in analyzing the role of deconditioning in HF patients. Indeed, a reduction of Q is one of the first events that provoke HF, and often it is first evident during exercise (1-3). Moreover, Q at peak exercise (peak Q) has a pivotal role in HF prognosis and in the assessment of HF treatment efficacy (3-6). Indeed, many HF treatments aim at improving Q, such as resynchronization therapy (7), mitral insufficiency correction, or some anti-failure drugs. Peak Q is analyzed either as Q alone or as Q included in oxygen uptake (VO_2) measurement (8), since Q = VO_2 / arteriovenous content difference [$\Delta(a\text{-}v)O_2$)]. However, given that it is difficult to directly measure peak Q, several peak Q estimation or surrogate parameters have been proposed, all of them with a modest clinical usefulness (9-14). Even in healthy subjects of different ages and genders, a reference normal value of peak Q is practically lacking. Indeed, data on directly measured peak exercise Q in healthy subjects are limited to a few historical reports built on a number of cases inadequate to draw any population-based normality references (15-24).

However, a prediction of peak Q in healthy subjects was described using a formula built on Higginbotham data (5, 15, 25, 26). This formula is: peak Q = 5 × predicted peak VO_2 + 3, and it was first used to define the lower value of normality (5, 25-27). This formula, however, was derived from data obtained in 24 healthy male individuals, so that its use as population reference is at least questionable (15). Accordingly, also the quantitative role of age and gender on peak Q is still questioned and basically unknown (19-21, 24, 28).

The inert gas rebreathing (IGR) technique allows non-invasive, reliable Q measurement at rest and during exercise both in healthy subjects and in HF patients (29-31), provided, in the latter subjects, that exercise-induced hemoglobin desaturation is limited or absent (32). In such a case, shunt estimation can be done,

but it adds some uncertainty (32). In any case, peak Q can be measured in healthy subjects by IGR, so that it is possible to do population studies and measure peak Q in different settings.

The present study was therefore undertaken to calculate peak Q in a sizable population of healthy subjects of different genders and ages and to define a formula that could estimate peak Q from measured peak VO_2.

METHODS

Study Population

We studied 500 voluntary normal subjects who performed a maximal cardiopulmonary exercise test (CPET) with Q measurement at peak exercise by IGR. Professional athletes were excluded as well as subjects who defined themselves as athletes. Subjects were recruited by public announcement or by word of mouth. Study inclusion criteria for normal subjects were: age range between 18 and 80 years, absence of present and past significant diseases, normal physical examination, normal electrocardiogram, no medical therapy regularly assumed with the exception of oral estroprogestin or thyroid replacement therapy, capability to perform a maximal CPET without signs or symptoms of any disease. Subjects were asked to refrain from smoking in the 6 hours before the test. All subjects underwent at least one teaching session, to understand and practice the IGR methodology. During the teaching session, multiple IGR maneuvers with and without gases were done. Subjects who were unable to perform the IGR technique were excluded from the present study.

The study complies with the Declaration of Helsinki, the locally appointed ethics committee approved the research protocol (approval number R435/16-CCM451), and informed consent was obtained from all subjects.

Study Design

All subjects underwent clinical evaluation associated with collection of health history and recent instrumental data.

All subjects underwent a cycle-ergometer CPET consisting of a personalized ramp protocol based on predicted maximum tolerance, with Q measurement by IGR at rest and at peak exercise. To avoid possible interferences of the IGR technique with peak VO_2 measurements, the latter always preceded Q measurements.

Ramp Protocol CPET

CPET was performed with a progressive work rate increase in a ramp pattern, after at least 3 minutes of rest and a brief (at least 2 minutes) unloaded cycling. Expiratory O_2, CO_2, and ventilation were measured breath by breath (Innocor® rebreathing system, Innovision A/S, Odense, Denmark). A 12-lead electrocardiogram was recorded (Quark T12x Cosmed, Roma, Italy). Subjects were strongly encouraged to perform a maximal test, but the maximum was self-determined when they approached maximal exercise, allowing the final 30 seconds for the rebreathing maneuver. The rate of work rate increase during the test was decided in order to achieve peak exercise in 8 to 12 minutes during the increasing work rate period. Peak VO_2 was reported as a mean over the last 20 seconds of exercise. Percentage of predicted peak VO_2 was calculated according to Wasserman et al. (33).

Q measurement

The IGR technique uses an oxygen-enriched mixture of an inert soluble gas (0.5% nitrous oxide-N_2O) and an inert insoluble gas (0.1% sulphur hexafluoride-SF_6) from a pre-filled bag (29-31). Subjects breathe into a respiratory valve via a mouthpiece and a bacterial filter with a nose clip. At the end of expiration, the valve is activated, so that subjects will rebreathe from the pre-filled bag for a period of 10-20 seconds. After this

period, subjects are switched back to ambient air, and Q measurement is terminated. Photoacoustic analyzers measure gas concentration over a 5-breath interval. SF_6 is used to determine lung volume. N_2O concentration decreases during rebreathing with a rate proportional to pulmonary blood flow (PBF), that is the blood flow that perfuses the ventilated alveoli. Q is equal to PBF when the arterial oxygen saturation measure (SpO_2) is high (> 98% using the pulse oximeter), showing the absence of pulmonary shunt flow. If SpO_2 < 98%, Q is equal to PBF+shunt flow. The latter can be estimated (29, 32). However, this was not needed in the present setting, since only normal subjects were studied.

Two experts independently read each test and evaluated the linearity of end-expiratory gas pressure decay, and the results were averaged.

Statistical Analysis

Data are expressed as means ± standard deviation; differences between males and females were compared by unpaired t-test, while differences between age groups (≤40 years versus 41-60 years versus >60 years) were compared by ANOVA and Bonferroni post hoc analysis as appropriate. Linear regression analysis was performed to assess the best fitting linear relationship between Q and peak VO_2, and between age and cardiac index (CI), peak VO_2 or Q.

Differences between linear regressions were evaluated by interaction.

The Bland and Altman method was applied to compare Q measured by IGR with Q estimated by Higginbotham formula.

All tests were two-sided, and a p value below 0.05 was considered as significant. All statistics were performed with SPSS for windows or SAS statistical package v.9.2 (SAS Institute Inc., Cary, NC).

RESULTS

Voluntary subjects were recruited until 500 had performed a maximal CPET (peak respiratory quotient = 1.12± 0.12) and a proper Q measurement at peak exercise by IGR. Consequently, 520 subjects were tested. Indeed, 20 subjects voluntarily interrupted the exercise before the IGR maneuver was completed or they did not perform a proper IGR measurement at peak exercise. Table 1 shows the anthropometric characteristics of the studied population. Resting Q and CI are reported in table 1. Peak VO_2 as % of the predicted value was 95± 18% in the entire population and 95± 19% and 95±18% in males and females, respectively. Peak VO_2 and peak Q values were higher in males than in females, both progressively decreasing with age (table 2). Similarly, peak exercise $\Delta(a\text{-}v)O_2$ was higher in males than in females, but it was unaffected by age (table 2).

Peak Q and peak VO_2 were strictly related either considering the overall population or considering males and females separately (figure 1, panel A and B). The Higginbotham formula applied to the 500 healthy subjects demonstrated a relevant dispersion of data compared to Q measured by IGR, and an average overestimation of peak Q (0.5±2.4 L/min), which was greater the lower the peak Q (figure 2).

The correlation between age and peak VO_2, both as an absolute value (mL/min) and normalized for body weight (mL/min/kg) in the entire population and considering males and females separately, is reported in table 3. The correlation between age and peak Q was present but relatively poor, however it improved considering the two genders separately. The correlation further improved when CI was used instead of Q, particularly in the female gender (table 3). In figure 3, the correlation between age and peak CI is reported adding the data from previous reports (12, 15-17, 19, 20, 23, 24, 34-36).

We also calculated O_2 pulse at peak exercise as peak VO_2 / peak HR. In figure 4, the correlation between O_2 pulse at peak exercise / peak exercise stroke volume is reported.

DISCUSSION

The present study showed that, in an unselected population of healthy individuals, peak VO_2 is strictly related to peak Q, and that it varies according to age and gender. This study allowed to provide an equation to predict peak Q from peak VO_2, showing that, in the general population, peak Q = 4.4 x peak VO_2 + 4.3, while it is 4.3 x peak VO_2 + 4.5 and 4.9 x peak VO_2 + 3.6 in males and females, respectively. The above-reported equations are obtained for the first time from a sizable population of normal subjects (n=500) who performed a maximal cycle ergometer exercise – for the entire population and for males and females separately. It is of note that several of the previously reported invasive Q measurements (12, 15, 17, 19, 20, 23, 24, 34, 36) fit with the IGR-obtained peak Q measurement.

Peak Q had been previously measured invasively in a few studies (12, 15-17, 19, 20, 23, 24, 34-36), which had mainly been done in young males. The various studies we were able to evaluate reported a total of 233 subjects in whom peak Q was measured, using direct Fick, thermo- or dye-dilution techniques. However, the subjects studied included a few athletes (n = 44), only 49 females and 66 subjects with an age >50 years. It should be noted that Julius et al. (19) studied 54 subjects including 19 female subjects, but data are reported only combined, so that gender-related differences cannot be separately assessed. Moreover, data on subjects over 50 years old were reported separately from those of younger cases only in Julius et al.'s report (19). All tests were done on a cycle ergometer except for those by Hossak et al. (24), who used a treadmill. For comparison, peak CI in Hossak's data was reduced by 10% (33). Accordingly, none of the above-reported studies, either alone or in combination, provides a reliable population-based measurement of peak exercise Q. Therefore, although the invasive measurement of peak Q remains the "gold standard", we performed the present study using the IGR technique, whose reliability has been previously assessed in several reports (29-31). Albeit with the limitation of a cross-sectional evaluation, the majority of the data fit with our measurements (figure 3), with the exception of Granath et al. (16) and Grimby et al.'s (35) reports, which showed a peak CI higher than expected. The explanation for this difference is uncertain , although Grimby et al tested middle-age, well trained active athletes (35) and Granath studied a small population with an average age of 71 (16). It should be noticed that, also applying the Higginbotham formula, Granath

and Grimby's results were significantly higher than expected. As generally believed, we confirmed that peak Q decreases as age increases, and it was lower in females when compared to males of the same age (37), regardless of gender-related differences in the mechanisms responsible for Q increase (28).

A few studies analyzed peak Q as a function of age, gender, and training in normal subjects using non-invasive estimates of Q (28, 38-40). A direct comparison of these reports' data with ours is not possible because of the limited number of subjects studied, different exercise ergometers, protocols, and Q estimation methods. However, also in these studies, older age and female gender were both associated with a lower peak Q (38, 39), while different exercise training levels were associated with a different peak exercise Q (40). Indeed, Ridout et al (38) found that peak Q was higher in men than in women , and that it significantly decreased with age in both sexes . Specifically, they reported a peak Q of 23.6±2.7 vs. 17.4±3.5 L/min in younger and older males, respectively, and 17.7±1.9 vs. 12.3±.6 L/min in younger and older females. Bogaard et al (39) showed a higher peak CI in young (age 20-30y) than in older subjects (age 50-60), 10.6±2.5 and 7.2±1.3 L/min/m2 ($p<0.0005$), respectively. Finally, Tomai et al (40) reported a similar peak CI in sedentary young male subjects and weight lifters (11.5±1.2 and 10.5±2.7 L/min/m2, p=ns), and a significant higher peak CI in swimmers (14.2±2.6 L/min/m2, $p<0.01$).

The knowledge of a normal peak exercise Q in the population is extremely important, particularly for comparisons with patients who show an exercise performance limitation. In clinical practice, several surrogates of peak exercise Q have been proposed, but the most frequently used is O_2 Pulse, which is calculated as peak VO_2 / peak heart rate. Actually, O_2 pulse is stroke volme x $\Delta(a\text{-}v)O_2$. The correlation found between O_2 pulse and stroke volume was strong (figure 4), suggesting a limited dispersion of $\Delta(a\text{-}v)O_2$ at peak exercise. However, the present VO_2-derived formula should not be used to estimate exercise Q or stroke volume in patients such as HF and COPD patients. Indeed, in HF patients, *peak VO_2 has a recognized pivotal role in the prognosis determination and in the decision making process(41, 42). However,* a low peak VO_2 may be due to several reasons on top of low Q, including muscle impairment, altered blood flow distribution to the exercising muscles, and anemia. Similarly, in COPD patients, on top of the above-reported causes of exercise limitation, hypoxia and ventilation constraint directly affect peak VO_2. The

Higginbotham formula has been frequently used to estimate peak Q from peak VO_2 (5, 25-27). Unfortunately, the Higginbotham formula was built on data obtained from 24 young males, a number unable to provide a general population evaluation. Moreover, the formula derived from Higginbotham measurements was built to calculate the lower limit of normality and not the average normal value. Regardless, we measured an average overestimation of peak Q by the Higginbotham formula (27).

Few study limitations should be acknowledged. Firstly, we measured peak Q only once in each subject. Consequently, we did not evaluate the intra-subject variability of peak exercise Q in this series of subjects. However, a very limited intra-subject variability has been previously shown with IGR technique in normal subjects and in HF patients (29, 43). Secondly, we did not assess peak Q changes with age or physical training in the same subject. Thirdly, the role of different feeding habits before exercise on exercise performance was not analyzed, nor was the role of cigarette smoking assessed. Furthermore, the utilization of the present formula to estimate peak Q from peak VO_2 in cases outside the frame of the present study should be done with caution, particularly in children and adolescents. Similarly, the application of our formula in subjects with an age at the edge of our population's, such as the elderly, should be done with caution. The same caution should be applied in case of well-trained subjects, since athletes were specifically excluded from the present study, or in case of particularly deconditioned subjects. A similar caution applies to obese subjects. Indeed, although obesity was not a study exclusion criterion, no obese subjects responded to our call. A study dedicated to obese subjects is definitely needed. Moreover, we studied exercise tests using a cycle-ergometer with peak exercise reached through a ramp exercise protocol in ~10 minutes. We do not know whether the present formula can be applied when using a different ergometer such as a treadmill or a different exercise protocol. Finally, our formula was built using maximal exercise tests, and it should not be applied in case of submaximal tests.

CONCLUSIONS

In conclusion, the present study describes peak exercise Q in a large population of normal subjects of different ages and genders, and it provides a formula to estimate Q from measured peak VO_2. It is intriguing to speculate that, in the near future, simultaneous measurements of both peak Q and VO_2 and knowledge of both predicted values will become of crucial relevance for the evaluation and treatment of subjects with exercise limitation such as HF patients. Indeed, for example in a HF patient, low peak VO_2 has a strong prognostic power (44), but it may be associated with low Q or preserved Q – in the former case, the failing heart becomes the first treatment target, while in the latter case periphery and in general non-heart-related deficiency should be the main treatment targets.

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Prof. Agostoni: Conception and design of the study, data analysis and interpretation, critical revision and manuscript preparation. He is guarantor of the paper, taking responsibility for the integrity of the work as a whole, from inception to published article.

Dr. Vignati: Design of the study, data collection, analysis and interpretation and manuscript preparation.

Dr. Gentile: Data collection, analysis and interpretation and manuscript preparation.

Dr. Boiti: Data collection and analysis.

Dr. Farina: Data collection, analysis and interpretation and manuscript preparation.

Dr. Salvioni: Data collection, analysis and interpretation and manuscript preparation.

Dr. Mapelli: Analysis and interpretation and manuscript preparation.

Dr. Magrì: Data collection, analysis and interpretation.

Dr. Paolillo: Data collection, analysis and interpretation and manuscript preparation.

Dr. Corrieri: Data collection, analysis and interpretation.

Prof. Sinagra: Data analysis and interpretation, critical revision and manuscript preparation.

Dr. Cattadori: Conception and design of the study, data analysis and interpretation, critical revision and manuscript preparation.

Finally, each Author gave their approval to the submission of this manuscript for publication.

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FIGURE LEGEND

Figure 1: Panel A: Relation between VO_2 (L/min) and cardiac output (L/min) at peak exercise. Best fitting linear regression between peak VO_2 and peak Q in the total population and separately in males (blue circles) and in females (pink circles).

Panel B: Relation between peak VO_2 (L/min/m^2) and cardiac index (L/min/m^2) at peak exercise. Symbols as in panel A.

Figure 2: Bland-Altman plot for cardiac output (Q).

Plot of the differences between Higginbotham formula and IGR method to measure Q in healthy subjects.

The dotted blue line identifies the linear relationship between differences and average values, the red line identifies the mean of the difference between the two techniques, the black lines express the mean ± 1.96 standard deviation.

Figure 3: Relation between age and cardiac index at peak exercise.

Linear regression between age and cardiac index in the studied population (n= 500 subjects). The circles represent data obtained in previous studies (12, 15-17, 19, 20, 24, 34-36, 45).

Figure 4: Relation between stroke volume (SV) and O_2 pulse at peak exercise in the total population and separately in males (blue circles) and in females (pink circles).

Table 1: Anthropometric characteristics of the studied population (n=500).

	All (n=500)			Males (n= 260)			Females (n=240)			p
Age (years)	45.0 range	±	13.5 18-77	45.2 range	±	13.1 18-77	44.7 range	±	13.8 21-75	ns
Weight (Kg)	68.6	±	13.3	77.2	±	10.3	59.4	±	9.5	<0.001
Height (cm)	171	±	9	177	±	7	164	±	6	<0.001
Hb (g/dl)	14.4	±	1.0	14.9	±	0.5	13.8	±	1.1	<0.001
Rest Q (L/min)	5.4	±	1.5	5.9	±	1.5	4.8	±	1.3	<0.001
Rest CI (L/min/m^2)	3.0	±	0.8	3.1	±	0.8	2.9	±	0.8	<0.05

Data are mean ± standard deviation. Q= Cardiac output; CI= Cardiac Index. Age distribution was: a) age 18-40 years 181/88/93 in the entire population and in males and females, respectively; age >40-60 aa 242/134/108; age >60-80 77/38/39.

Table 2: Data at peak exercise in the total population and by gender.

		Peak VO_2 (mL/min)	Peak Q (L/min)	Peak Δ(a-v) (mL/100mL)	Peak HR (bpm)	Peak SV (mL)	Peak CI (L/min/m^2)
Total Population	All (n=500)	2025±668	13.2±3.5	15.2±2.7	157±19	84.5±21.6	7.33±1.59
	M (n=260)	2494±560	15.3±3.4	16.5±2.7	158±20	96.7±20.3	7.87±1.69
	F (n=240)	1518±309	11±2.1	13.8±2	156±18	71±13.7	6.75±1.24
	p M vs. F	<0.001	<0.001	<0.001	NS	<0.001	<0.001
Age ≤40	All(n=181)	2175±688#	14.4±3.4*y	15±2.5	168±14*y	86.2±19.9z	8.15±1.46*y
	M (n=88)	2735±532	16.9±2.9	16.3±2.5	170±16	100.1±16.9	8.82±1.57
	F (n=93)	1646±277	12.1±1.8	13.7±1.8	167±13	73±12.2	7.52±1.02
	p M vs. F	<0.001	<0.001	<0.001	NS	<0.001	<0.001
Age 41-60	All(n=242)	2042±655#	13.1±3.4y	15.5±2.8	155±17y	85.1±22.6	7.13±1.41y
	M (n=134)	2485±515	15.1±3.1	16.7±2.8	156±18	96.7±21.2	7.64±1.45
	F(n=108)	1492±292	10.7±1.9	14±2	153±17	70.5±14.4	6.49±1.05
	p M vs. F	<0.001	<0.001	<0.001	NS	<0.001	<0.001
Age>60	All (n=77)	1627±483	10.8±2.7	15.1±3	139±20	78.9±21.5	6.04±1.37
	M (n=38)	1969±392	12.2±2.9	16.5±2.9	139±22	89.1±22.5	6.49±1.51
	F (n=39)	1286±283	9.5±1.7	13.7±2.4	140±17	68.8±14.9	5.59±1.06
	p M vs. F	<0.001	<0.001	<0.001	NS	<0.001	<0.01
ANOVA (entire population by age group)	p	<0.001	<0.001	ns	<0.001	0.043	<0.001

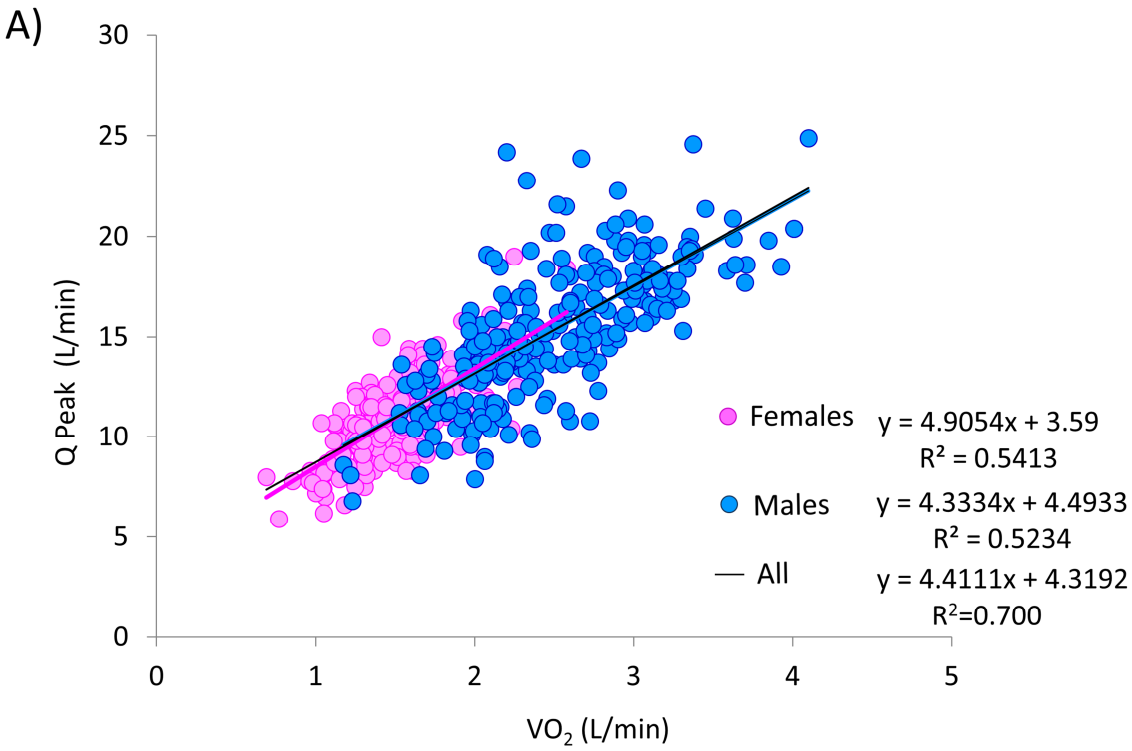
Data are mean ± standard deviation. M= Males; F= Females; VO_2= Oxygen uptake; Q= Cardiac output; Δ(a-v)= Arteriovenous O_2 differences, HR= Heart rate; SV= Stroke volume; CI= Cardiac Index

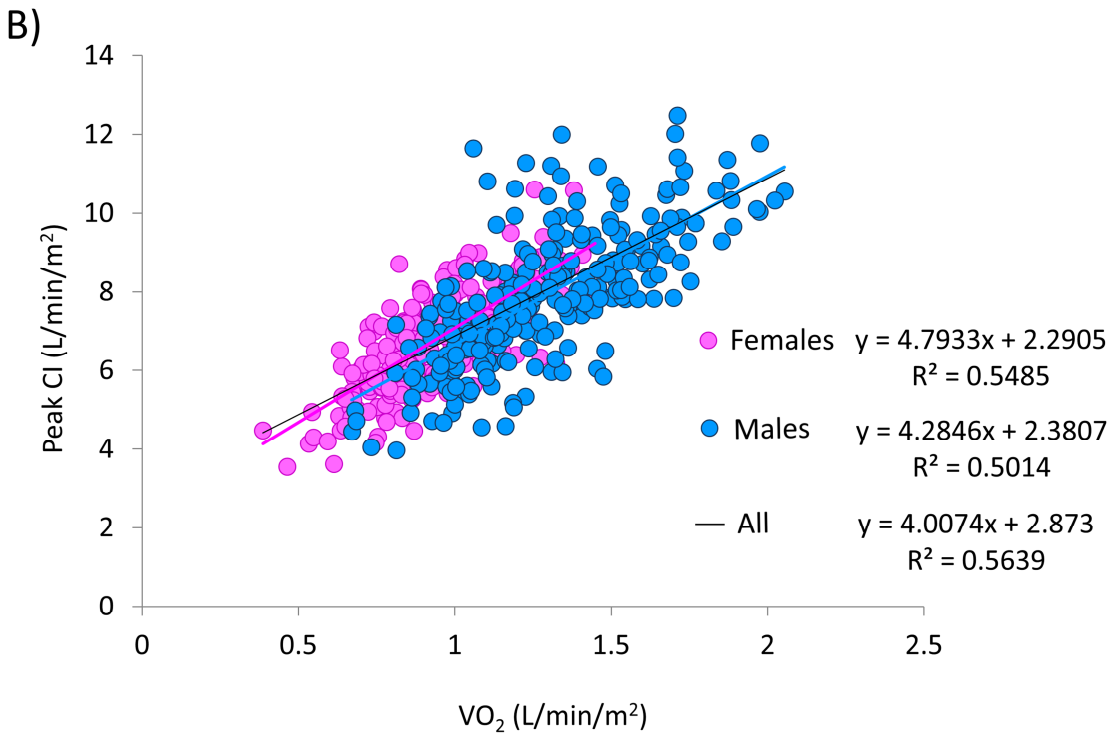
Bonferroni post hoc (entire population by age group):*: p<0.01 vs Age 41-40; y: p<0.01 vs Age>60; z:p<0.05 vs Age >60

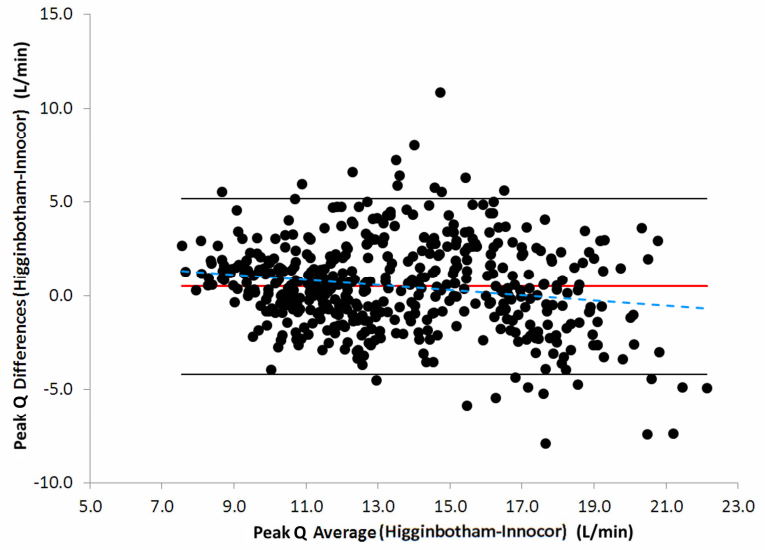
Table 3: Correlations between Age and VO_2, CO and CI at peak exercise

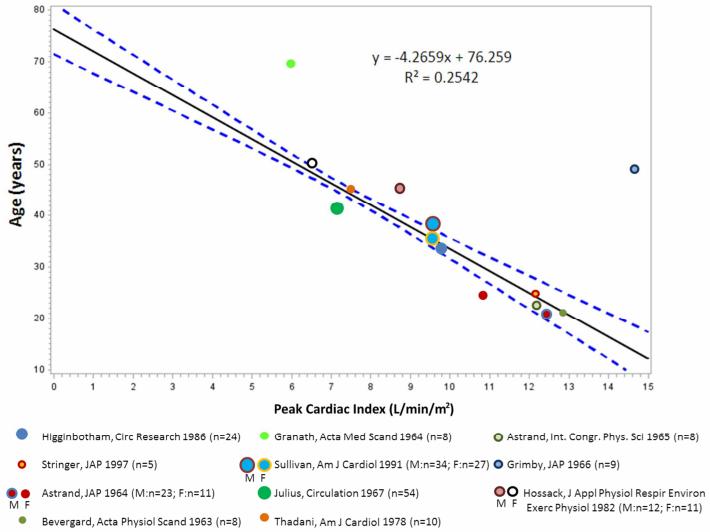
		R^2	p	equation
Age vs. peak VO_2	All	0.082	<0.001	Age=-5.78×peakVO_2+56.69
	M	0.225	<0.001	Age=-0.01×peakVO_2+73.04
	F	0.198	<0.001	Age=-0.02×peakVO_2+74.85
Age vs. peak Q	All	0.144	<0.001	Age=-0.10×peakQ+17.72
	M	0.261	<0.001	Age=-0.13×peakQ+21.19
	F	0.257	<0.001	Age=-0.08×peakQ+14.10
Age vs. peak CI	All	0.254	<0.001	Age=-4.27×peakCI+76.26
	M	0.263	<0.001	Age=-3.99×peakCI+76.75
	F	0.379	<0.001	Age=-6.86×peakCI+90.93
Age vs. peak dAV	All	0.002	ns	Age=0.24×peak Δ(a-v)O_2+41.39
	M	0.003	ns	Age=-0.25×peak Δ(a-v)O_2+41.14
	F	0.001	ns	Age=0.22×peak Δ(a-v)O_2+41.63

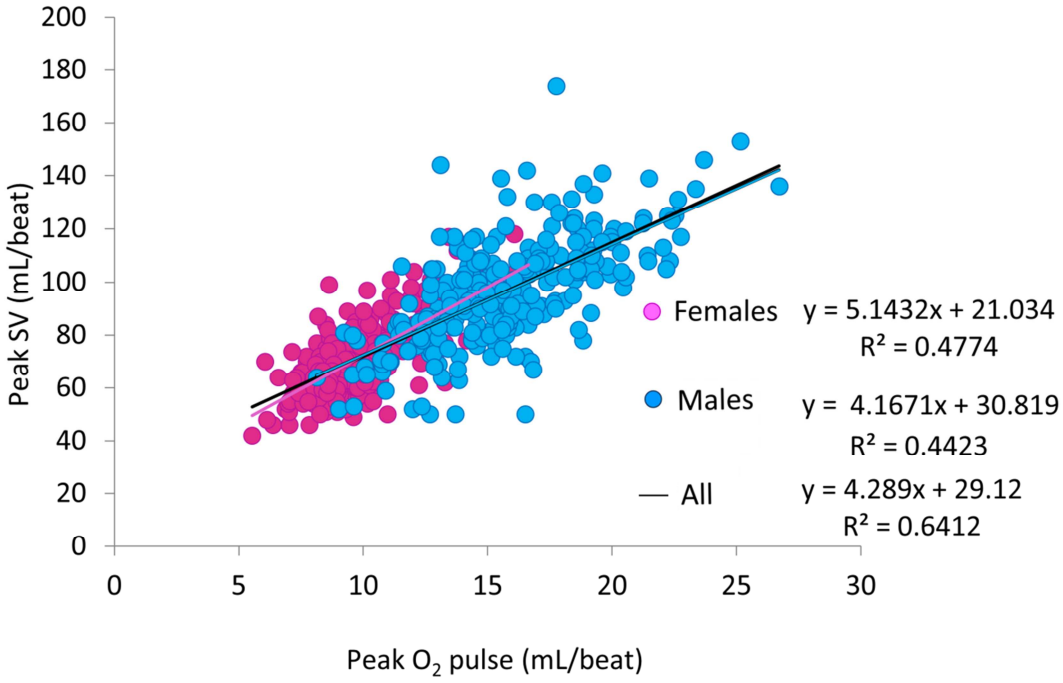
M= Males; F= Females; VO_2= Oxygen uptake; Q= Cardiac output; CI= Cardiac Index; Δ(a-v)O_2= arteriovenous difference


A)
Q Peak (L/min)
VO2 (L/min)
Females
y = 4.9054x + 3.59
R² = 0.5413
Males
y = 4.3334x + 4.4933
R² = 0.5234
All
y = 4.4111x + 4.3192
R²=0.700


B)
Peak CI (L/min/m²)
VO2 (L/min/m²)
Females
y = 4.7933x + 2.2905
R² = 0.5485
Males
y = 4.2846x + 2.3807
R² = 0.5014
All
y = 4.0074x + 2.873
R² = 0.5639







ABBREVIATIONS LIST

- Cardiac output (CO)
- Heart failure (HF)
- Oxygen uptake (VO2)
- Inert gas rebreathing (IGR)
- Cardiopulmonary exercise test (CPET)
- Pulmonary blood flow (PBF)
- Arterial oxygen saturation (SpO2)
- Cardiac Index (CI)